ICU MANAGEMENT & PRACTICE

ICU Volume 12 - Issue 4 - Winter 2012/2013 - Matrix Features

A Review of the Evolving Paradigm Shift in Intensive Care Unit Sedation Practices

Most mechanical ly vent i lated, cri t ical ly i l l adul ts wi l l require some degree of sedation during their intensive care unit (ICU) stay, an area which has been experiencing significant change in recent years. The goal of this article is to afford a concise, stateof- the-art review of the evolving paradigm shift in ICU sedation practices; current indications for prolonged, uninterrupted, and/or deep ICU sedation; clinical pharmacology of commonly used sedatives, including the novel sedative agent dexmedetomidine; comparative efficacy and safety of sedative agents as reported by systemat ic reviews and meta-analyses; and cost considerat ions regarding sedative agents used in the ICU.

Although prolonged, deep, and/or uninterrupted sedation has long been believed to be indicated for many ICU patients, this belief is now changing. As the technology of mechanical ventilation has evolved with time, is has become increasingly possible for critically ill adults to be awake and interactive while receiving assisted ventilation (Roberts et al. 2012). This shift in the paradigm of ICU sedation has been supported by several randomised controlled trials (RCTs), which have reported that sedation interruption or limitation may be associated with improved outcomes (Roberts et al. 2012).

An Evolving Paradigm Shift in ICU Sedation Practices

Evolution in assisted ventilation over time has made it increasingly feasible for intensivists to avoid neuromuscular blockade and limit the degree of sedation afforded to mechanically ventilated, critically ill adults (Roberts et al., 2012). Sedation interruption may reduce accumulation of sedative drugs and their active metabolites and prevent prolonged sedative drug effects or over-sedation (Augustes & Ho, 2011). Moreover, some RCTs have reported that sedation limitation or interruption may reduce requirements for neurological investigations such as head computed tomography scans, and decrease the length of mechanical ventilation or ICU stay (de Wit et al. 2008; Girard et al. 2008; Kress et al. 2000; Mehta et al. 2008; Schweickert et al. 2009; Strom et al. 2010; Strom et al. 2011). Despite these potential benefits, concerns regarding the practice of sedation interruption remain These include the possibility of patient discomfort or anxiety, inadvertent removal of the endotracheal tube or central venous catheter, and increased nursing workload (Augustes and Ho 2011; Mehta et al. 2012; Roberts et al. 2012).

In an attempt to better characterise the comparative efficacy and safety of daily sedative interruption among critically ill adults, Augustes and Ho conducted a systematic review and meta-analysis of RCTs in 2011. They identified five RCTs of daily sedative interruption (Anifantaki et al. 2009; de Wit et al. 2008; Girard et al. 2008; Kress et al. 2000; Mehta et al. 2008), which enrolled a total of 669 critically ill adults, and used opioids in combination with midazolam or a mixture of benzodiazepines and propofol for analgo-sedation. Although this meta-analysis reported that daily sedative interruption was safe and may reduce the risk of tracheostomy among critically ill medical and surgical patients, it suffered from several limitations. These include the small number of included patients and the possibility of a type II error in their findings, inconsistency or imprecision in their reported effect estimates, significant heterogeneity in their pooled effect estimates, and the lack of long term data on mortality or other patient-important outcomes (Augustes and Ho 2011). Finally, although a small observational study suggested that daily sedative interruption may be safe among critically ill adults at risk for coronary artery disease (Kress et al. 2007), the meta-analysis by Augustes and Ho was unable to specifically analyse the outcomes of these patients given that they were uncommonly included in the reviewed RCTs (Augustes and Ho 2011).

Although avoiding prolonged, deep sedation may improve outcomes, several RCTs have questioned whether sedative interruption is the optimal means of achieving sedation limitation. A recent multi-centre RCT found no difference in median time to successful extubation, duration of ICU and hospital stay, or delirium among 430 medical and surgical critically ill adults allocated to either protocolised light sedation or protocolised light sedation plus sedation interruption (Mehta et al. 2012). Moreover, the sedation interruption group received more opioids and benzodiazepines, and nurses self-assessed their workload as being higher (Mehta et al. 2012). In a second RCT that compared a protocol of no sedation to daily sedative interruption, the no sedation group was reported to have had a shorter duration of mechanical ventilation and hospital and ICU stay (Strom et al., 2010). However, the no sedation group was observed to have had a significantly higher risk of agitated delirium (Strom et al. 2010).

Thus, while it remains unclear which method of sedation limitation (i.e. sedative interruption or limitation via a sedation protocol or other means) is most optimal, it is becoming increasingly obvious that over-sedation is harmful for critically ill adults, and should generally be avoided (Roberts et al. 2012).

Indications for Prolonged, Uninterrupted, and/or Deep ICU Sedation

In certain situations prolonged, uninterrupted, and/or deep ICU sedation may still be appropriate (Roberts et al. 2012). Indications for this approach include:

1. Requirement for alternate ventilation strategies, neuromuscular blockade, or extracorporeal membrane oxygenation for management of significant hypoxemia or hypercarbia;

2. Management of agitation, intracranial hypertension, and airway secretions among those with severe traumatic brain injury (TBI) or other causes of reduced intracranial compliance;

3. Cardiogenic shock as a result of myocardial ischemia or infarction, in order to reduce myocardial oxygen demand; and

4. Certain agitated intoxications associated with an increased risk of harm to self or others (Brodie and Bacchetta 2011; Levine et al. 2011; Pipeling and Fan 2010; Roberts et al. 2011; Roberts et al. 2012; Sanborn and Feldman 2004).

Clinical Sedative Agent Pharmacology

Most available sedative drugs produce their effects by activation of either the gamma-amino-butyric-acid type A (GABAA) receptor (benzodiazepines, volatile anesthetic agents, and propofol) or the alpha-2 adrenergic receptor (dexmedetomidine) (Roberts et al. 2012). GABAA receptor stimulation produces dose-dependent anxiolysis, amnesia, muscle relaxation, sedation, hypnosis, seizure threshold elevation, decreased level of consciousness, and respiratory depression (Devlin and Roberts 2011; Roberts et al. 2012). Activation of the alpha-2 adrenergic receptor produces sedation and may lead to bradycardia and hypotension (Gerlach and Dasta 2007; Hoy and Keating 2011; Roberts et al. 2012).

An understanding of sedative pharmacokinetics is required to achieve an adequate level of sedation for several reasons. Critically ill adults often develop dysfunction of one or more organs involved in drug elimination. Moreover, sedative agents are prone to numerous drug-drug and drug-disease interactions, and their half-lives are often context sensitive. Therefore, critically ill adults exhibit inter- individual variability in sedative drug response, and their dosage regime must therefore be frequently adjusted. This is best accomplished using a tool for sedation assessment, such as the Richmond Agitation Sedation Scale (RASS), and adjusting sedation levels accordingly. Although this topic has clinical relevance, its discussion is complex; therefore, interested readers should refer to more comprehensive reviews.

Although several sedative agents have been used among critically ill adults, below is a discussion of the clinical pharmacology and pharmacotherapeutics of only those that are commonly used or newly available.

Benzodiazepines

Benzodiazepines (diazepam, lorazepam, and midazolam) are frequently used sedatives and differ mostly in terms of their pharmacokinetics (Mehta et al. 2006; Roberts et al. 2012). Midazolam has a significantly more rapid onset and offset of action than lorazepam. Moreover, midazolam and diazepam are more prone to drug interactions than lorazepam as these agents are metabolised by the cytochrome P450 (CYP450) enzymes CYP3A4/CYP2C19 and CYP3A4, respectively. Diazepam and midazolam also have active metabolites that may accumulate in renal failure or during prolonged, uninterrupted intravenous infusions.

Benzodiazepines have several associated adverse drug reactions. These include delirium, hypotension, respiratory depression, and a withdrawal syndrome associated with acute discontinuation. Lorazepam has been associated with paradoxical agitation, and may precipitate in intravenous line tubing if not diluted to a concentration <1mg/ml before administration. Finally, as vials of lorazepam contain propylene glycol, this drug may produce propylene glycol toxicity, which often manifests as an elevated osmolar gap metabolic acidaemia associated with acute tubular necrosis.

Propofol

Propofol is a commonly used sedative and ultra-short acting intravenous anaesthetic agent that has sedative, anxiolytic, and amnestic effects (Roberts et al. 2012). The drug has a very rapid onset of action. Although time to recovery from sedation with this drug is shorter than that for benzodiazepines, its exact duration of action is context-sensitive and dose-dependent, with clearance of the drug occurring through hepatic and extrahepatic glucuronidation and sulphation.

Propofol-related adverse drug reactions include injection-site pain during peripheral intravenous administration, bacterial infection or bacteraemia, respiratory depression leading to apnea, hypotension, and hyperlipidaemia, which may induce acute pancreatitis (Devlin et al. 2005; Devlin et al. 2010; Roberts et al. 2012). Propofol infusion syndrome, characterised by metabolic acidaemia, refractory bradycardia, hyperkalaemia, rhabdomyolysis, hyperlipidaemia, and fatty hepatomegaly is a rare but potentially lethal complication of propofol sedation (Roberts et al. 2012). Management of propofol infusion syndrome includes discontinuation of the drug and supportive management, including use of temporary cardiac pacing when necessary (Roberts et al. 2012).

Dexmedetomidine

Dexmedetomidine is a novel, highly selective, alpha-2 receptor agonist that has sedative, analgaesic, and anxiolytic properties (Roberts et al. 2012). The drug has been approved for sedation of adult ICU patients in North America and Europe. Advantages of dexmedetomidine over other sedative agents include its seemingly lower risk of drug-associated delirium (Gerlach and Dasta, 2007; Pandharipande et al. 2007; Roberts et al. 2012). The drug has also been associated with a reduction in the required dosage of other sedatives and decreased time to extubation when compared with other intravenous sedatives (Riker et al. 2009; Roberts et al. 2012; Venn et al. 1999). As dexmedetomidine is metabolised in the liver by CYP2A6 and N-glucuronidases, dosage reduction should be considered in patients with hepatic impairment (Roberts et al. 2012). Common adverse effects of dexmedetomidine include bradycardia and hypotension (Roberts et al. 2012). As such, the drug is rarely given as a bolus dose, and is instead slowly titrated up to 0.2-0.7 mcg/kg/hour, and then increased in 30-minute intervals until desired sedative effects are achieved (Roberts et al. 2012).

Efficacy and Safety of Sedative Agents as Reported by Systematic Reviews and Meta-Analyses

No large RCTs yet exist comparing light sedation with one sedative agent versus another; thus,when choosing between agents, physicians must rely largely on the outcome data previously reported in RCTs of continuous or deeper sedation. Therefore, in an attempt to compare the efficacy and safety of individual drugs, we examined the evidence presented in systematic reviews and meta-analyses that compared two or more sedative drugs or a sedative drug versus placebo (Ho and Ng, 2008; Magarey 2001; Ostermann et al. 2000; Roberts et al. 2011; Walder et al. 2001).

The findings of these studies, in combination with those of a recent structured and comprehensive review of all of the available evidence on sedation for critically ill or injured adults (Roberts et al. 2012), allow for several general conclusions to be made. First, no sedative agent appears to be associated with an improved mortality among critically ill adults or those with severe TBI (Roberts et al. 2012). Moreover, although most sedative agents (except opioid analgaesics) appear to improve intracranial pressure and cerebral perfusion pressure among mixed populations of patients with severe TBI, no drug appears to improve neurologic outcome (Roberts et al. 2011). While propofol and midazolam appear to produce a largely similar quality of sedation among critically ill adults, propofol may be associated with an accelerated weaning time after discontinuation of sedation and possibly a shortened duration of mechanical ventilation (Roberts et al. 2012). However, in contrast to midazolam, propofol increases the risk of hypotension, hyperlipidaemia, and possibly bradycardia. Finally, while dexmedetomidine appears to be associated with a lower risk of drug-associated delirium, this drug increases the risk of hypotension and bradycardia, and has not yet been evaluated among mechanically ventilated adults with TBI (Roberts et al. 2011; Roberts et al. 2012).

Cost Considerations

Although several studies have examined the cost-effectiveness of alternate sedative agents and reported variable results, several factors must be considered when examining these studies (Roberts et al. 2012). These include the drugs' acquisition costs, the efficacy and safety of the sedative, and the setting of the cost effectiveness analysis (including the healthcare system in which it was conducted) (Roberts et al. 2012).

Interested readers may refer to a recent structured review by our group that presented the results of individual cost-effectiveness analyses and an approach to their interpretation (Roberts et al. 2012).

Conclusions

An evolving paradigm shift from deep, prolonged, and\or uninterrupted ICU sedation towards a sedation strategy that limits the degree of sedation is occurring in critical care medicine (Roberts et al. 2012). Although it remains unclear which method of sedation limitation (i.e. sedative interruption, limitation via a sedation protocol, or other means) is most optimal for critically ill adults, over-sedation appears to be harmful and should be avoided (Roberts et al. 2012). However, in certain situations, prolonged, uninterrupted, and/or deep ICU sedation may still be appropriate, such as for management of intracranial hypertension after severe TBI (Roberts et al. 2012). Future research should aim to clarify the indications for limited versus prolonged, uninterrupted, and/or deep sedation, and to define the most appropriate method and agent(s) to be used for sedation limitation among critically ill adults.

Published on : Thu, 7 Mar 2013